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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,368	09/20/2001	Mieko Katsuura	447.001	8538

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,368	KATSUURA ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0501*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (encompassing claims 1, 2, 4, 6, 8, 12, and 13) is acknowledged. The traversal is on the ground(s) that the proteins are structurally related and have a common antagonistic mechanism. In addition, Applicant noted that the restriction requirement did not include claims 14 and 15 which were submitted with the preliminary amendment filed March 28, 2001.

Applicant's arguments have been fully considered and have been found to be persuasive. Claims 3, 5, 7, 9-11 and 13-15 will be examined with the claims of Group I. Claims 1-15 are pending and under consideration.

Specification

The use of the trademarks NUCLEOSIL™ (p. 13) and PICO-TAG™ (p. 15) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for MP52 polypeptides modified at methionine or tryptophan residues that act as MP52 or BMP-2 antagonists, does not reasonably provide enablement for modified MP52 polypeptides, modified BMP-2 polypeptides, modified BMP-4 polypeptides or modified BMP-7

polypeptides that act as antagonists against any bone morphogenetic protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1-15 are drawn to proteins having antagonistic activity against any bone morphogenetic protein (BMP) and methods of using such proteins for the treatment of ectopic ossification or metabolic diseases with ossification. Applicants teach a modified form of human MP52 that is able to act as an antagonist to human BMP-2 (see p. 12). However, Applicants have not provided examples of proteins that can act as antagonists to all BMPs.

The BMPs are divided into three subgroups: (1) BMP-2 and BMP-4; (2) BMP-5, BMP-6, and BMP-7; and (3) BMP-3 (Wozney (1992), *Mol. Reprod. Dev.* 32(2): 160-167). BMPs function by interacting with unique combinations of type I and type II BMP receptors (Xiao *et al.* (2002), *J. Bone Miner. Res.* 17(1): 101-110). In addition, members of the BMP family show different affinities to the different combinations of type I and type II BMP receptors (Yamashita *et al.* (1996), *Bone* 19(6): 569-574). Applicants teach modifying MP52, BMP-2, BMP-4, or BMP-7 at methionine or tryptophan residues located in each protein's receptor binding site, however, because BMPs interact with unique combinations of receptors and because BMPs have different affinities to different combinations of receptors, one of skill in the art would not expect modified forms of BMP-2 or BMP-4 to be effective antagonists against BMP-7 or other BMPs. The claims are not enabled for modified forms of MP52, BMP-2, BMP-4 or BMP-7 that are antagonists against every kind of BMP.

Claims 1-15 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus, *i.e.* modified BMPs that are antagonists to all BMPs. Applicants have disclosed a modified form of MP52 that is an antagonist to MP52 and BMP-2, but have not disclosed sufficient species for the broad genus of any modified BMP that is an antagonist to all BMPs.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of MP52 or BMP-2 antagonists that are derived from modified forms of MP52, Applicants were not in possession of modified forms of MP52 or any other kind of BMP wherein the modified protein was an antagonist to all members of the BMP family. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore, only MP52 proteins with methionine or tryptophan residues converted or replaced with hydrophilic or polar residues that are MP52 or BMP-2 antagonists but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1, 2, 4, 5, 8, and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an MP52 protein modified at residues 30, 71, or 74 that is an antagonist to BMP-2, does not reasonably provide enablement for an MP52 protein modified at residue 111 alone that is an antagonist to BMP-2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 2, 4, 5, 8, and 12-15 are drawn to proteins having an antagonistic activity against BMPs by replacing at least one residue among the methionine residues located at positions 30, 71, 74, and 111 of SEQ ID NO: 1 with a hydrophilic or polar amino acid residue.

The specification teaches that residues 30, 71 and 74 are located in the receptor binding site, and by modifying the residues in the receptor binding site the protein would be converted to an antagonist (see p. 6 of specification). The methionine at position 111 is not located in the receptor binding site. The claims encompass proteins wherein only the methionine at position 111 is replaced with a hydrophilic or polar amino acid residue. One of skill in the art would not expect such a protein to be an effective BMP antagonist, because residue 111 is not within the receptor binding site. Thus, the claims are not enabled for proteins wherein only the methionine at position 111 is replaced with a hydrophilic or polar amino acid residue.

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

Canalis *et al.* (2003), *Endocrine Reviews* 24: 218-235

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
6/14/04